Synopsis – Study 15906A

Study Title An interventional, randomised, double-blind, parallel-group, placebo-controlled, active-referenced (paroxetine), fixed-dose study on the efficacy of vortioxetine on cognitive dysfunction in working patients with major depressive disorder
Investigators 18 principal investigators at 18 sites in 4 countries *Signatory investigator* – [redacted]
Study Sites 18 sites – 3 in Estonia, 5 in Finland, 5 in Germany, and 5 in Lithuania
Publications None (as of the date of this report)
Study Period *First patient first visit* – 20 October 2014 (the date when the first *Informed Consent Form* was signed) *Last patient last visit* – 5 February 2016 (the date of the last protocol-specified contact with any patient)
Objectives • *Primary objective*: – to assess the efficacy of acute treatment with 10 mg/day vortioxetine *versus* placebo on cognitive performance (focusing on the aspect concerning speed of processing, executive functioning, and attention) in working patients with major depressive disorder (MDD) • *Secondary and exploratory objectives*: – to assess the efficacy of vortioxetine *versus* placebo on: • cognitive dysfunction (performance and subjective reporting) • depressive symptoms • clinical global status • functionality and quality of life • work productivity – to assess the proportion of the treatment effect on cognitive dysfunction, that is not attributed to an improvement in depressive symptoms – to assess the safety and tolerability of vortioxetine – to assess the efficacy and safety of the active reference (paroxetine) *versus* placebo on all the same parameters as mentioned for vortioxetine
Study Methodology • This was an exploratory, interventional, prospective, multi-national, multi-site, randomised, double-blind, parallel-group, placebo-controlled, active-reference, fixed-dose study. • The study consisted of: – a 4 to 10-day Screening Period – an 8-week Core Treatment Period – a 4-week Safety Follow-up Period, of which the first week was a taper-down period

Study Methodology (continued)

- At baseline, the patients were randomised equally (1:1:1) to double-blind treatment with fixed doses of either vortioxetine (10 mg/day), paroxetine (20 mg/day), or placebo. Patients who completed the 8-week, double-blind treatment period entered a 1-week, double-blind taper-down period: patients treated with vortioxetine or placebo received placebo; patients treated with paroxetine received 10 mg/day of paroxetine.
- During the Core Treatment Period, patients were seen at Weeks 1, 4, and 8, at which efficacy and safety data were collected; at Week 6, the investigator contacted the patient directly by phone, in order to verify the patient's status.
- Patients who withdrew were seen for a Withdrawal Visit as soon as possible. Treatment with the 1-week, double-blind, down-taper medication was to be offered to patients who withdrew.
- A safety follow-up visit/contact was done approximately 4 weeks after the Completion/Withdrawal Visit.

Number of Patients Planned

150 patients were planned for randomisation: 50 in the vortioxetine group, 50 in the paroxetine group, and 50 in the placebo group

Diagnosis and Main Selection Criterion

Outpatients with a primary diagnosis of recurrent MDD according to DSM-IV-TR™ (classification 296.3x), as confirmed using the Mini International Neuropsychiatric Interview (MINI), who:

- had a Montgomery-Åsberg Depression Rating Scale (MADRS) total score ≥26 at the Screening Visit and at the Baseline Visit
- had had the current major depressive episode (MDE) for ≥3 months
- were ≥18 and ≤65 years of age
- were employed full or part-time (defined as minimum 50% full-time working hours per week)
- had been in the current job/position for ≥3 months

Investigational Medicinal Product, Dose and Mode of Administration, Batch Numbers

Vortioxetine – 10 mg/day; encapsulated tablets, orally; batch No. 2391955

Reference Therapies, Doses and Mode of Administration, Batch Numbers

Placebo – powder-filled capsules, orally; batch No. E103662-0003E

Paroxetine (Seroxat®) – 10 or 20 mg/day; encapsulated tablets, orally; batch No. 030 (10 mg) and 670M (20 mg)

Duration of Treatment

8 weeks of double-blind treatment followed by a 1-week double-blind down-taper period.

Efficacy Assessments

- Neuropsychological tests and performance-based functionality
  - Digit Symbol Substitution Test (DSST)
  - Trail Making Test A (TMT-A)
  - Trail Making Test B (TMT-B)
  - Simple Reaction Time (SRT)
  - Choice Reaction Time (CRT)
  - Stroop Colour Naming Test (STROOP)
  - University of San Diego Performance-based Skills Assessment – Brief (UPSA-B)
- Patient-reported cognitive function
  - Perceived Deficits Questionnaire – Depression (PDQ-D)
- Depressive symptoms and clinical global impression
  - Montgomery and Åsberg Depression Rating Scale (MADRS)
  - Clinical Global Impression – Global Improvement (CGI-I)
  - Clinical Global Impression – Severity of Illness (CGI-S)

Efficacy Assessments (continued)

- Clinician-rated functionality
  - Functioning Assessment Short Test (FAST)
- Health-related Quality of Life and Work Productivity
  - EuroQoL 5 Dimensions (EQ-5D-3L)
  - Work Limitation Questionnaire (WLQ)

Genomic/Metabolomic/Proteomic Assessments

- Blood sampling for gene expression profiling
- Blood sampling for metabolomic/proteomic biomarkers
- Blood sampling for pharmacogenetics

The results of the genomic and metabolomic/proteomic assessments are not included in this *Clinical Study Report.*

Safety Assessments

- Adverse events (AEs)
- Columbia Suicide Severity Rating Scale (C-SSRS)

Endpoints

- *Primary endpoint*:
  - cognitive performance:
    - change from baseline to Week 8 in the DSST (number of correct symbols; domains affected: attention, speed of processing, and executive functioning)
- *Key secondary endpoint:*
  - functionality:
    - change from baseline to Week 8 in UPSA-B total score
- *Secondary endpoints*:
  - cognitive dysfunction, neuropsychological tests:
    - change from baseline to Week 8 in TMT score (TMT-A; speed of processing and TMT-B; executive functioning)
    - change from baseline to Week 8 in reaction time score (CRT; attention and SRT; psychomotor speed)
    - change from baseline to Week 8 in STROOP score (incongruent; executive functioning and congruent score; speed of processing)
  - cognitive dysfunction, patient-reported:
    - change from baseline to Week 8 in PDQ-D total score
  - depressive symptoms and clinical global impression:
    - change from baseline to Week 8 in MADRS total score
    - change from baseline to Week 8 in CGI-S score
    - CGI-I score at Week 8
  - functionality, clinician-rated:
    - change from baseline to Week 8 in the FAST total score
- *Exploratory endpoints*:
  - change from baseline to all visits, where assessed, in the neuropsychological tests (DSST, TMT-A, TMT-B, STROOP, SRT, CRT), PDQ-D total and subscale scores, MADRS total score, CGI-S score, FAST, WLQ, and EQ-5D-3L scores.
  - CGI-I score, MADRS and CGI-I response, and MADRS and CGI-S remission at all visits where assessed.
  - change from baseline to all visits where assessed (Weeks 1 and 8) in the overall cognition composite z-score (defined as the weighted sum of the z-scores in the DSST, TMT-A, TMT-B, STROOP, SRT, and CRT)

Endpoints (continued)

- *Safety endpoints*:
  - adverse events
  - C-SSRS categorisation based on Columbia Classification Algorithm of Suicide Assessment (C-CASA) definitions (1, 2, 3, 4 and 7)

Statistical Methodology

- The following analysis sets were used:
  - *all-patients-randomised set* (APRS) – all randomised patients
  - *all-patients-treated set* (APTS) – all patients in the APRS who took at least one dose of (IMP)
  - *full-analysis set* (FAS) – all patients in the APTS who had a valid baseline assessment and at least one valid post-baseline assessment of the DSST (number of correct symbols)
- Unless otherwise indicated, the efficacy analyses were based on the FAS and the safety data were summarised based on the APTS.
- *Analyses of the primary endpoint*
  - The primary endpoint was analysed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) approach. The model include the following fixed effects: site group, week (Weeks 1 and 8), and treatment (vortioxetine 10 mg/day, paroxetine 20 mg/day and placebo) as factors, baseline DSST score (number of correct symbols) as a continuous covariate, treatment-by-week interaction, and baseline score-by-week interaction.
  - An unstructured covariance structure was used to model the within-patient errors. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. The analysis was based on the missing-at-random (MAR) assumption and performed using all available observations (observed cases [OC] data) in the Core Treatment Period.
  - The mean differences between treatment groups were estimated based on the least squares means for the treatment-by-visit interaction in the MMRM model. The estimates are presented with p-values and 95% confidence intervals (CIs). The primary comparison is the contrast between vortioxetine 10 mg/day and placebo at Week 8.
  - A sensitivity analysis using a pattern-mixture model was performed, in which missing values due to withdrawal from treatment in all treatment groups were imputed using sequential regression-based multiple imputations based on the placebo group. 1000 simulations were performed using a random seed 8734275. The 1000 complete datasets were analysed using the MMRM model specified above. The different estimated treatment effects and standard errors across the datasets were combined to produce a unique point estimate and standard error, taking into account the uncertainty of the imputation.
  - A sensitivity analysis of the primary endpoint was also performed using an analysis of covariance (ANCOVA) model by week using the last observation carried forward (LOCF) and OC, including site group and treatment as factors, and baseline score as a continuous covariate. The mean difference between vortioxetine 10 mg/day and placebo was estimated from the model based on the least squares means for treatment. The estimates are presented with p-values and 95% CIs.
  - The potential influence of covariates was investigated with an ANCOVA (LOCF and OC) as above by adding main terms for covariates and interaction terms with treatment to the model. The covariates investigated were sex, age, body mass index (BMI), job type, and country.
- *Analyses of the key secondary endpoint*
  - The key secondary endpoint was analysed with an ANCOVA model. The model was based on using the LOCF and included site group and treatment as factors and baseline UPSA-B total score as a continuous covariate.
  - The mean differences between treatment groups were estimated based on the least squares means for the treatment factor in the ANCOVA model. The estimates are presented with p-values and 95% CIs. The primary comparison is the contrast between vortioxetine 10 mg/day and placebo.

Statistical Methodology (continued)

- *Analyses of the key secondary endpoint*
  - A sensitivity analysis of the key secondary endpoint was performed using the same ANCOVA model as specified above, but excluding patients with a baseline UPSA-B total score of 100, since this is the maximal obtainable score in UPSA-B.
  - In addition, a sensitivity analysis using a pattern-mixture model type approach was performed, in which missing values due to withdrawal from treatment in all treatment groups were imputed using sequential regression-based multiple imputations based on the placebo group. 1000 simulations were performed using a random seed 4432142. The 1000 complete datasets were analysed using the ANCOVA model specified above. The different estimated treatment effects and standard errors across the datasets were combined to produce a unique point estimate and standard error, taking into account the uncertainty of the imputation. This analysis was performed based on the APRS. The ANCOVA LOCF analysis was repeated for completers.
  - The potential influence of covariates was investigated with an ANCOVA (LOCF and OC) as above by adding main terms for covariates and interaction terms with treatment to the model. The covariates investigated were sex, age, age, BMI, job type, and country.
- *Testing strategy*
  - A hierarchical testing procedure was used, testing at the 5% level to control the type 1 error. The hierarchy included the primary comparison, vortioxetine 10 mg/day *versus* placebo, of the primary and key secondary endpoints. The testing only continued to the key secondary endpoint if statistical significance was reached for the primary endpoint.
- *Analyses of the secondary endpoints*
  - The secondary endpoints were analysed with a MMRM similar to the model specified for the primary endpoint. In addition, ANCOVA (OC and LOCF) was performed per visit with treatment and grouped site as factors and baseline score as a covariate.
- *Analyses of the exploratory endpoints*
  - Continuous and categorical exploratory endpoints (changes from baseline) were analysed with a MMRM similar to the model specified for the primary endpoint. In addition, ANCOVA (OC and LOCF) was performed per visit, with treatment and grouped site as factors and baseline score as a covariate.
  - Response and remission was analysed by week (FAS, LOCF) using logistic regression with treatment as factor and baseline score as a covariate. This was supplemented by a similar analysis based on OC. Additional sensitivity analyses, where a patient having a missing value at the week analysed was classified as a non-responder/non-remitter, were performed using the same logistic regression.
  - For associations between functionality and endpoints addressing cognitive dysfunction, the analysis was performed for the Week 8 assessments by estimating a partial correlation coefficient, where the set of controlling variables included treatment group and baseline values for the respective variables. Association for the same outcomes at baseline was done with a Pearson correlation coefficient.
  - To assess the effect of early improvement in DSST on later improvement in MADRS total score, an exploratory analysis of change from baseline to Week 8 in MADRS total score was modelled with an ANCOVA (OC) including treatment and site group as factors and with baseline MADRS total score, baseline DSST number of correct symbols, change from baseline to Week 1 in MADRS total score and change from baseline to Week 1 in DSST number of correct symbols as continuous covariates.
  - In a path analysis performed *post hoc*, the potential treatment effect on cognitive dysfunction was separated into a direct effect and an indirect effect that is mediated through an improvement in depression. These effects were estimated for the cognition composite z-score using two ANCOVA models.
- *Safety endpoints*
  - Adverse events and C-SSRS data were summarised using descriptive statistics.

Patient Disposition and Analysis Sets

• Patient disposition is summarised below:

	PBO		VOR 10mg		PAR 20mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients randomised	49		48		55		152	
Patients treated (all-patients-treated set [APTS])	48		48		54		150	
Patients completed	46	95.8	41	85.4	47	87.0	134	89.3
Patients withdrawn	2	4.2	7	14.6	7	13.0	16	10.7
Primary reason for withdrawal:								
Adverse event(s)	1	2.1	3	6.3	3	5.6	7	4.7
Lack of efficacy	1	2.1	2	4.2	1	1.9	4	2.7
Other	0		2	4.2	3	5.6	5	3.3
Analysis sets:								
APTS	48		48		54		150	
Full-analysis set (FAS)	48		48		52		148	

Demography and Baseline Characteristics of the Study Population

• Two-thirds of the patients in the APTS were women and the mean age of the patients was 46 years. All patients except 2 were White. The treatment groups were comparable with respect to age, sex, and race.

• There were no relevant differences between the treatment groups in social history (level of education, marital and employment status, and living arrangements), drinking and smoking habits, family psychiatric history, or traumatic life events.

• The mean number of previous MDEs was approximately 2 in all treatment groups. The mean duration of the current MDE ranged between 27 and 37 weeks across the treatment groups.

• The mean baseline efficacy scores were generally comparable across the treatment groups. The overall mean PDQ total score of 39 points, and the mean MADRS total scores of 31 points correlated well with *moderate* to *severe* MDD.

Efficacy Results

Primary and Key Secondary Endpoints

• The results of the testing strategy are summarised below:

Cognitive Function Endpoints	Change from Baseline to Week 8		Difference to Placebo at Week 8 (FAS)			
	N	Mean (SE)	Difference (SE)	95% CI	p-value	Effect Size[a]
Primary endpoint: DSST Score						
Placebo	47	7.37 (1.06)				
Vortioxetine	46	7.59 (1.08)	0.22 (1.51)[b]	-2.76; 3.20	0.8845	0.03
Paroxetine	48	6.61 (1.05)	-0.76 (1.49)[b]	-3.70; 2.18	0.6091	-0.105
Key secondary endpoint: UPSA-B Total Score						
Placebo	47	5.33 (1.11)				
Vortioxetine	46	5.75 (1.13)	0.42 (1.57)[c]	-2.69; 3.54	0.7894	0.06
Paroxetine	50	5.95 (1.08)	0.62 (1.53)[c]	-2.42; 3.65	0.6884	0.08

a Standardised effect size was calculated as the difference from placebo.
b MMRM
c ANCOVA, LOCF

• In the DSST, there was an improvement (increase) in the mean number of correct symbols in all treatment groups after 8 weeks of treatment. The MMRM estimates for the mean change from baseline to Week 8 in the DSST number of correct symbols was 7.6 in the vortioxetine group and 6.6 in the paroxetine group; these changes were not statistically significant relative to that seen in the placebo group (7.4).

Efficacy Results (continued)

Primary and Key Secondary Endpoints (continued)

- The UPSA-B score increased (improved) in all treatment groups after 8 weeks of treatment. In the ANCOVA, the mean change from baseline to week 8 in the UPSA-B total score was 5.75 in the vortioxetine group and 5.95 in the paroxetine group; these changes were not statistically significant relative to that of the placebo group (5.3).
- Since the p-value for the primary endpoint was >0.05, the testing strategy was stopped. For analyses outside the testing strategy, statistical significance was based on nominal p-values with no adjustment for multiplicity.

Cognitive Function

- At Week 8, the patients in both the vortioxetine group and the paroxetine group showed an improvement (decrease) in the mean cognitive function scores for TMT (A and B), SRT, CRT, and STROOP (congruent and incongruent). In the MMRM, the mean differences to placebo were numerically in favour of vortioxetine for all tests. For the SRT, which had a standardized effect size of 0.55 *versus* placebo, the mean difference to placebo was statistically significant at Week 8 for the vortioxetine group. The results observed in the paroxetine group were not statistically significantly different from those in the placebo group for any of the neuropsychological tests at Week 8. The results of the MMRM analyses were supported by the ANCOVA, LOCF and OC analyses. The results of the neuropsychological test at Week 1 showed a similar pattern to those obtained at Week 8.
- For the overall cognition composite z-score, the mean difference to placebo was statistically significant in the vortioxetine group at Week 8 using the MMRM. A similar effect on the cognition composite z-score was not observed in the paroxetine group; this was confirmed in a *post hoc* analysis which showed a statistically significant improvement for the vortioxetine group relative to paroxetine at Week 8 (MMRM).
- The patients in both the vortioxetine and the paroxetine groups reported a greater improvement in self-perceived cognitive function, measured using PDQ-D total and subscale scores, compared to placebo. At Week 8, the mean difference to placebo was statistically significant for both treatment groups for the PDQ-D total score and for most subscales.

Depressive Symptoms and Clinical Global Impression

- The patients in both the vortioxetine and the paroxetine groups improved in the depressive symptom and clinical global impression variables (MADRS total score, CGI-S and CGI-I scores, and proportions of responders and remitters) throughout the 8-week Core Treatment Period. These improvements were statistically significant relative to the placebo group at Weeks 4 and 8 in the MMRM analyses, the ANCOVA, LOCF and OC, and in the logistic regression analyses for both vortioxetine and paroxetine.

Functionality and Quality of Life

- In addition to the UPSA-B, functionality was also assessed using the clinician-rated FAST. The patients in the vortioxetine group showed an improvement in the FAST total score at Week 8 that was statistically significantly different to that of the placebo group (MMRM, ANCOVA [LOCF and OC]).
- In the patient-reported quality of life assessment, EQ-5D, there was an improvement in both the EQ-5D utility index and in the overall health state visual analogue scale (VAS) at Week 8 for all treatment groups; the improvement in the overall health state VAS was statistically significant relative to placebo in the paroxetine group (MMRM).

Work Productivity

- There was an improvement (decrease) in the patient-reported WLQ Productivity Loss Score relative to baseline for all treatment groups. For the vortioxetine group, the change from baseline in the WLQ Productivity Loss Score was statistically significant relative to placebo at Week 8 in the ANCOVA, OC analysis. For the paroxetine group, the change from baseline was statistically significant relative to placebo at Week 8 in both the MMRM and the ANCOVA analyses.

Safety Results

- The adverse event incidence in the Entire Study Period is summarised below:

	PBO		VOR 10mg		PAR 20mg	
	n	(%)	n	(%)	n	(%)
Patients treated	48		48		54	
Patients who died	0		0		0	
Patients with treatment-emergent serious AEs (SAEs)	1	(2.1)	0		2	(3.7)
Patients with treatment-emergent adverse events (TEAEs)	18	(37.5)	28	(58.3)	23	(42.6)
Total number of SAEs	1		0		2	
Total number of TEAEs	25		48		46	

- No deaths occurred during the study. A total of 3 patients had SAEs: 2 patients in the paroxetine group (calculus urinary and brain contusion) and 1 patient in the placebo group (pyelonephritis). None of the SAEs were considered to be related to IMP by the investigator.
- In the Entire Study Period, the overall incidence of adverse events was 58% in the vortioxetine group and 43% in the paroxetine group compared to 38% in the placebo group.
- In the Core Treatment Period, the TEAEs with an incidence ≥5% and with a higher incidence in the vortioxetine group than in the placebo group were nausea (placebo: 2.1%; vortioxetine: 38%; paroxetine: 17%) and headache (placebo: 4.2%; vortioxetine: 15%; paroxetine: 5.6%).
- The vast majority of the patients with TEAEs had *mild* or *moderate* TEAEs. The incidence of *severe* TEAEs was low; a total of 4 patients had *severe* TEAEs: 1 patient in the placebo group and 3 patients in the paroxetine group.
- One patient (2.1%) in the placebo group, 3 patients (6.3%) in the vortioxetine group, and 2 patients (3.7%) in the paroxetine group had adverse events leading to withdrawal. The most frequent TEAE leading to withdrawal was nausea (2 patients, both in the vortioxetine group).
- Based on the C-SSRS, 8.3% of the patients in the placebo group, and 4.2% and 3.7% of the patients in the vortioxetine group and the paroxetine groups, respectively, had suicidal ideation during the study; the majority of the patients were classified in the mildest category (*wish to be dead*) and none of the patients had suicidal ideation with an intent to act.

Conclusions

- Based on the pre-specified testing strategy, treatment with 10 mg/day vortioxetine did not reach statistical significance for the primary efficacy variable, change from baseline in DSST number of correct symbols at Week 8, relative to placebo in working patients with MDD.
- In general, 10 mg/day vortioxetine numerically improved executive function, attention, memory, and processing speed, relative to placebo, as assessed using a range of objective neuropsychological tests as well as subjective patient-reported cognitive function outcome. At Week 8, the difference to placebo was statistically significant for the patient-reported PDQ-D, and for the objective measures SRT and the overall cognition composite z-score.
- In the UPSA-B, 10 mg/day vortioxetine did not differentiate from placebo, whereas vortioxetine treatment statistically significantly separated from placebo in the clinician-rated functioning test, FAST.
- Treatment with 10 mg/day vortioxetine statistically significantly improved depressive symptoms and clinical global impression relative to placebo.
- In the patient-reported quality of life (EQ-5D) and work productivity assessments (WLQ), 10 mg/day vortioxetine showed a greater numerical, but not statistically significant, improvement relative to placebo.
- Vortioxetine 10 mg/day was safe and well tolerated in working patients with MDD.

Report Date

14 December 2016

This study was conducted in compliance with the principles of *Good Clinical Practice*.